Targeting FUS for Neuroprotection: a Novel Therapeutic in Amyotrophic Lateral Sclerosis

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Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease, with ~15% of cases being familial. Mutations in the fused in sarcoma (FUS) gene contribute to a subset of these cases. FUS is an RNA-binding protein that normally resides in the nucleus, where it participates in DNA repair, transcription, RNA splicing, and mRNA transport. However, under stress or when mutations disrupt its nuclear translocation signal (NTS), FUS mislocalizes to the cytoplasm, forming non-amyloid aggregates or associating with mitochondria. ALS pathogenesis likely involves both a toxic cytoplasmic gain-of-function and nuclear loss-of-function, though the dominant mechanism remains unclear. We identified a FUS-interacting compound, MC16, using click chemistry, and confirmed binding via NMR, MST, and SPR. MC16's effects were examined in cell lines overexpressing wildtype (WT) and NTS-mutant FUS (495X, 521C, 521G) and in Drosophila expressing human FUS variants (WT, 518K, 521C). MC16 significantly increased nuclear localization of NTS-mutant FUS (via GFP imaging and Western blot) and reduced FUS-Hsp60 association, indicating decreased mitochondrial targeting. In Drosophila, FUS expression in the compound eye caused ommatidia and bristle defects; MC16-fortified food ameliorated these phenotypes and increased nuclear FUS levels. Transcriptomic analysis revealed MC16-induced changes in genes regulating mitochondrial homeostasis and antioxidant responses.These findings suggest MC16 mitigates cytoplasmic FUS toxicity and restores protective nuclear functions. MC16 represents a potential therapeutic strategy for FUSopathies and other neurodegenerative or aging-related diseases involving mitochondrial dysfunction.

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